Pharmacogenetics of Antidepressants

The Role of Pharmacogenetics in Personalizing the Antidepressant and Anxiolytic Therapy

by **Milica Radosavljevic** [1,†], **Dubravka Svob Strac** [2,†], **Jasna Jancic** [3] and **Janko Samardzic** [1,*]

[1] Institute of Pharmacology, Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Belgrade, 11000 Belgrade, Serbia

[2] Laboratory for Molecular Neuropsychiatry, Division of Molecular Medicine, Rudjer Boskovic Institute, 10000 Zagreb, Croatia

[3] Clinic of Neurology and Psychiatry for Children and Youth, Faculty of Medicine, University of Belgrade, 11000 Belgrade, Serbia

[*] Author to whom correspondence should be addressed.

[†] These authors contributed equally to this work.

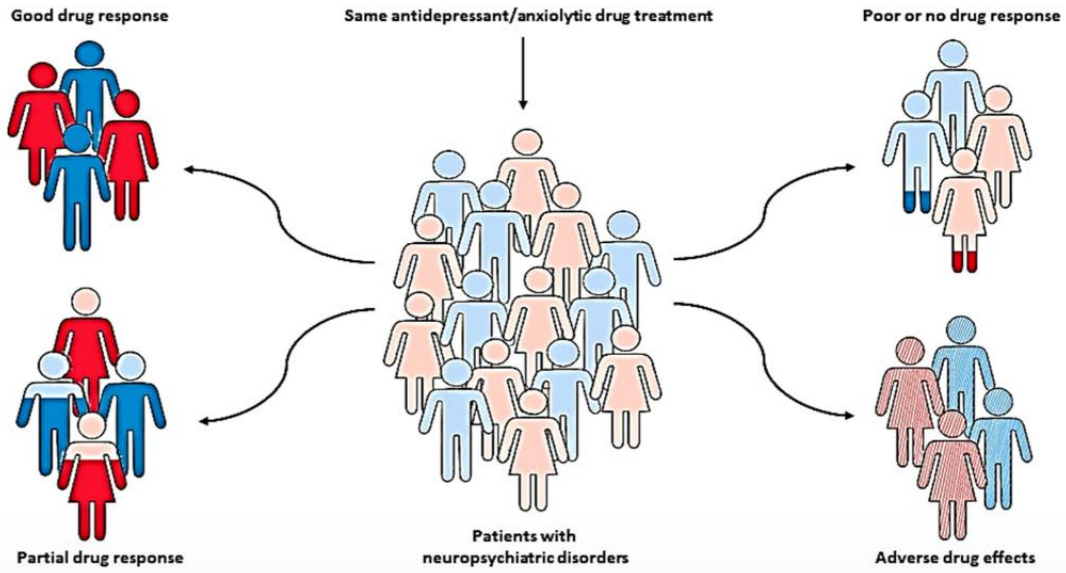
Genes **2023**, *14*(5), 1095; **https://doi.org/10.3390/genes14051095**

Pharmacogenetics of Antidepressants

The pharmacotherapy of neuropsychiatric disorders, such as anxiety and depression, has been characterized by significant **inter-individual variability** in drug response and the development of severe adverse effects, which has been recognized as a major clinical problem.

In addition to various environmental, physiological, and psychological factors, these individual differences might be largely due to genetic factors.

Therefore, **various pharmacogenetic studies have been conducted to identify genetic variants** that can predict patients who may optimally benefit from specific, individually tailored treatments



Pharmacogenetic studies have focused primarily on candidate genes involved in **drug metabolism and transport** (pharmacokinetics) as well as **drug action** (pharmacodynamics), which can influence both treatment efficacy and the development of adverse drug effects.

However, **pharmacogenetics is not able to explain all observed heritable variations in drug responses**, and there is growing evidence that responses to drugs could be influenced by individual **epigenetic** states

CYP2D6 variants

- The majority of ADs (fluoxetine; fluvoxamine; paroxetine; venlafaxine; mirtazapine; amitriptyline; imipramine; trimipramine; desipramine; nortriptyline) are metabolized primarily by CYP2D6

Table

CYP450 enzymes involved in biotransformation of SSRIs

SSRI	Enzymes involved in biotransformation
Citalopram	CYP2C19, CYP2D6, CYP3A4
Escitalopram	CYP2C19, CYP2D6, CYP3A4
Fluoxetine	CYP2D6, CYP2C9, CYP2C19, CYP3A4
Fluvoxamine	CYP1A2, CYP2D6
Paroxetine	CYP2D6, CYP3A4
Sertraline	CYP2C9, CYP2C19, CYP2D6, CYP3A4

CYP: cytochrome P450; SSRI: selective serotonin reuptake inhibitors

Source: Reference 10

CYP2D6

- CYP2D6 is the most researched gene in the field of pharmacogenetics, and more than 100 different alleles were identified which determine the level of activity of the enzyme

According to the number of gene copies inherited, individuals are classified as :

- poor (PM),
- intermediate (IM),
- extensive (EM), or
- ultrarapid metabolizers (UM).

Dose adjustment according to CYP2D6 phenotypes

Farmaco	Metabolizzatori Lenti (PM)	Metabolizzatori Intermedi (IM)	Metabolizzatori Rapidi (EM)	Metabolizzatori Ultrarapidi (UM)
Amitriptilina	-50/70% ↓	-25/50% ↓	Nessun adattamento	+50/100% ↑
Nortriptilina	-50/70% ↓	-25/50% ↓	Nessun adattamento	+50/100% ↑
Imipramina	-50% ↓	-25/50% ↓	Nessun adattamento	+50/100% ↑
Paroxetina	-50% ↓	-25% ↓	Nessun adattamento	+50% ↑
Venlafaxina	-30/50% ↓	-25% ↓	Nessun adattamento	+50% ↑

Legenda: ↓ riduzione della dose, ↑ incremento della dose.

This adjustments must be followed by clinical observation to evaluate the individual response and by the therapeutic monitoring of the drugs

CYP2D6 genetic test is recommended when:

- Resistant patients to the drug: when patients do not respond to normal dosage, the test could allow the doctor to find higher dosage to administer
- Serious or rare ADRs occur: the genetic test could explain if the gene variants is present and is responsible
- Complex polytherapy: the genetic test could avoid drug-drug interaction
- Narrow therapeutic index: the genetic test allows the right and safe choice of dosage

The combination between the genetic test and the therapeutic monitoring of the plasmatic drug level is essential to optimize and personalized the therapy.

Limitations to dose adjustment approach:

- Individual clinical variability: other factors (age, weight, concomitant diseases, drug-drug interaction….) can influence drug response
- Heterogeneity of the studies: different results could arise from the general population, thus reducing the generalizability of the results
- Pro-drugs: active metabolites are responsible of the clinical effects, thus the dose adjustment could be not enough to obtain the right response.
- Costs and accessibility: the costs of the tests are diminishing but their diffusion is limited for economic, commercial reasons and also depending on the presence of the clinical personnels able to interpret the data

CYP1A2

- A gene x environment effect has been shown concerning the CYP1A2 izoenzyme, in which the presence of an exogenous inducer, tobacco smoke affects transcription and translation and may contribute to an UM phenotype, resulting in an up to 50% reduction in plasma concentration of Ads
- Some CYP1A2 polymorphisms (rs4646425; rs2472304; rs2470890) may also influence treatment response to paroxetine

The CYP1A2 enzyme, encoded by the *CYP1A2* gene, is responsible for the metabolism of approximately **24% of antidepressant drugs**, including agomelatine, escitalopram, venlafaxine, duloxetine, and mirtazapine

The CYP1A2*1C variant is associated with **reduced enzyme activity → increased agomelatine level (side effects)**

The CYP1A2 *1F and *1B variants are associated with **increased enzyme activity → reduced agomelatine effect**

Several SNPs in the CYP1A2 gene, such as rs2069521, rs4646425, and rs4646427 polymorphisms, were associated with altered escitalopram metabolism (**reduced metabolisms function**) and an increased risk of adverse effects, such as fatigue and nausea/vomiting, particularly during the initial stages of treatment

CYP1A2 SNPs, such as rs4646425, rs2472304, and rs2470890, are associated with a **slower response** to paroxetine treatment

The rs2470890 polymorphism might be related to venlafaxine treatment remission

CYP2C19 variants

Drugs that are mainly metabolized by CYP2C19 include SSRIs such as escitalopram, citalopram, and sertraline.

The CYP2C19*1 allele variant is associated with **normal function**

The CYP2C19*17 variant **increases** CYP2C19 enzymatic **capacity**

CYP2C19*2 and *3 variants are responsible for the **loss of enzyme function**

A cross-sectional observational retrospective study, which included over **700 psychiatric patients**, revealed that **77% of patients** have at least one allele variant significantly affecting drug metabolism, with roughly **half of the individuals with reduced CYP2D6 enzyme** function and **the majority of them being CYP2C19 rapid and ultrarapid metabolizers.**

Therefore, due to their clinical relevance, both CYP2D6 and CYP2C19 are included in pharmacogenetics guidelines and recommendations published by the Clinical Pharmacogenetics Implementation Consortium (CPIC), Dutch Pharmacogenetics Working Group (DPWG), and regulatory agencies such as the FDA

Article | Open access | Published: 19 July 2024

Metabolic activity of CYP2C19 and CYP2D6 on antidepressant response from 13 clinical studies using genotype imputation: a meta-analysis

Danyang Li, Oliver Pain, Chiara Fabbri, Win Lee Edwin Wong, Chris Wai Hang Lo, Stephan Ripke, Annamaria Cattaneo, Daniel Souery, Mojca Z. Dernovsek, Neven Henigsberg, Joanna Hauser, Glyn Lewis, Ole Mors, Nader Perroud, Marcella Rietschel, Rudolf Uher, Wolfgang Maier, Bernhard T. Baune, Joanna M. Biernacka, Guido Bondolfi, Katharina Domschke, Masaki Kato, Yu-Li Liu, Alessandro Serretti, the GSRD Consortium, the Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, … Cathryn M. Lewis ✉ + Show authors

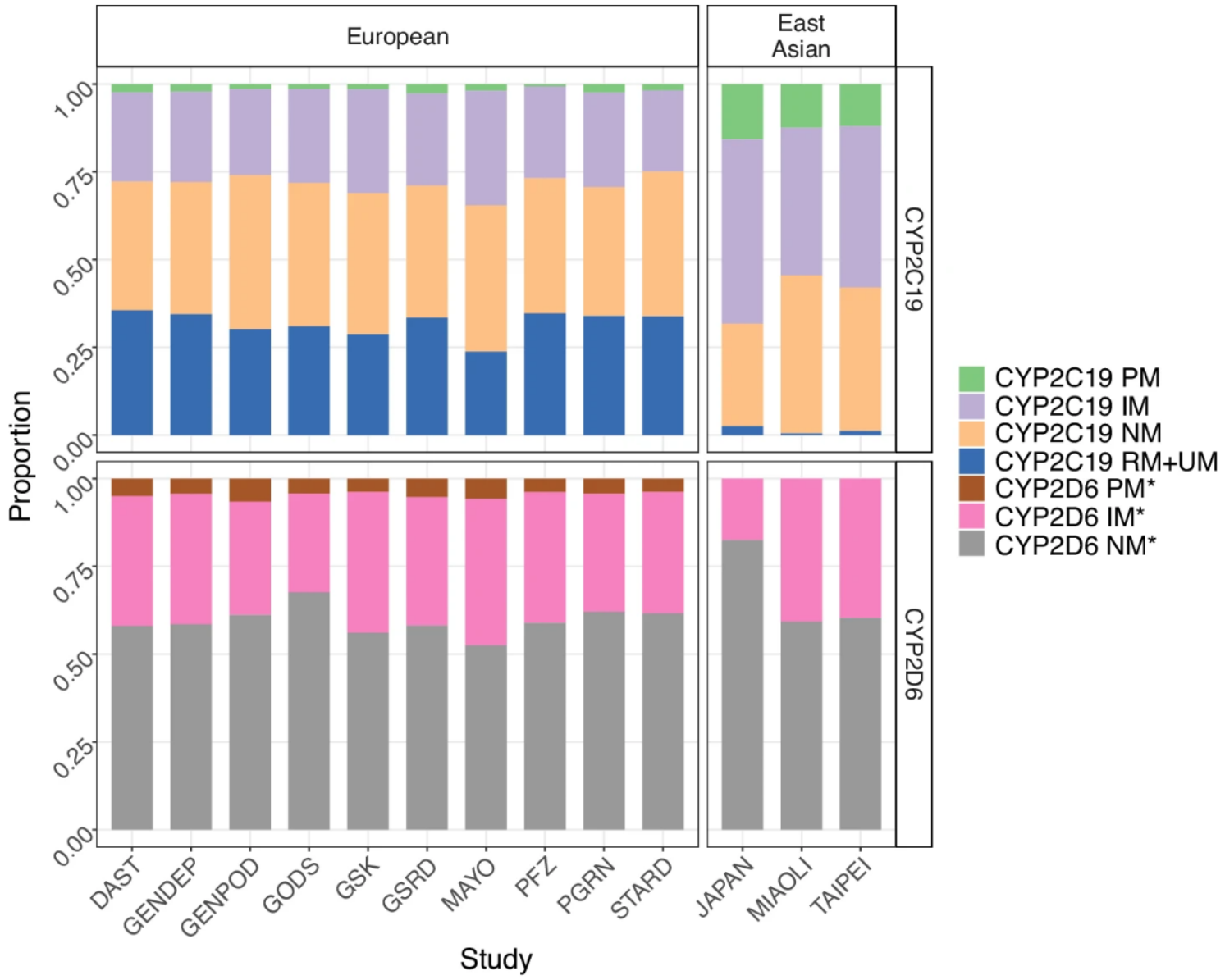
Translational Psychiatry **14**, Article number: 296 (2024) | Cite this article

AIM: to understand the impact of **genetic variations** on antidepressant response (remission or percentage improvement).

13 studies of European and East Asian ancestry populations were collected.

Fig. 1: Proportion of metabolic phenotypes in each cohort.

From: Metabolic activity of CYP2C19 and CYP2D6 on antidepressant response from 13 clinical studies using genotype imputation: a meta-analysis



Imputed genotype was used to translate genetic polymorphisms to metabolic phenotypes (poor, intermediate, normal, and rapid+ultrarapid) of CYP2C19 and CYP2D6.

***CYP2D6* structural variants** cannot be imputed from genotype data, limiting the determination of metabolic phenotypes, and precluding testing for association with response.

The association of CYP2C19 metabolic phenotypes with treatment response was examined using normal metabolizers as the reference.

Among 5843 depression patients, **a higher remission rate was found** in **CYP2C19 poor metabolizers** compared to normal metabolizers at nominal significance but did not survive after multiple testing correction (OR = 1.46, 95% CI [1.03, 2.06], p = 0.033, heterogeneity I2 = 0%, subgroup difference p = 0.72).

In conclusion, using imputed genotype data, our meta-analysis showed **no significant association between CYP2C19 metabolic phenotypes with antidepressant response**.

Moderate evidence of an association with **CYP2C19 poor metabolizers** was indicated, which **had higher rates of antidepressant remission**.

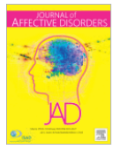
Metabolic phenotypes of **CYP2C19 differed in frequency** between European and East Asian populations but did **not differ in their effect on treatment outcomes**.

Metabolic phenotypes imputed from genetic variants using genotype were not associated with antidepressant response.

Research studies with genotype are limited in their assessment of pharmacogenetic variation especially for CYP2D6.

Fuller assessment of metabolizer status together with information on clinical factors and broader ancestry diversity could reduce the heterogeneity and improve power to evaluate the effect of metabolic phenotypes on antidepressant response.

Journal of Affective Disorders
Volume 395, Part A, 15 February 2026, 120724



Research paper

Longitudinal impact of CYP2D6 and CYP2C19 metabolizer status on antidepressant response: The role of Pharmacogenetic mismatch

Alessandro Serretti [a b], Stefano Barlati [c d], Lisa Buson [e], Valentina Menesello [e f], Anna Magistrali [f], Rosana Carvalho Silva [f], Giulia Perusi [e], Gabriele Nibbio [d], Stefano Bignotti [g], PANDORA study group [1], Giovanni Battista Tura [g], Antonio Vita [c d], Raffaele Ferri [b], Chiara Fabbri [h], Massimo Gennarelli [e f], Alessandra Minelli [e f]

Show more

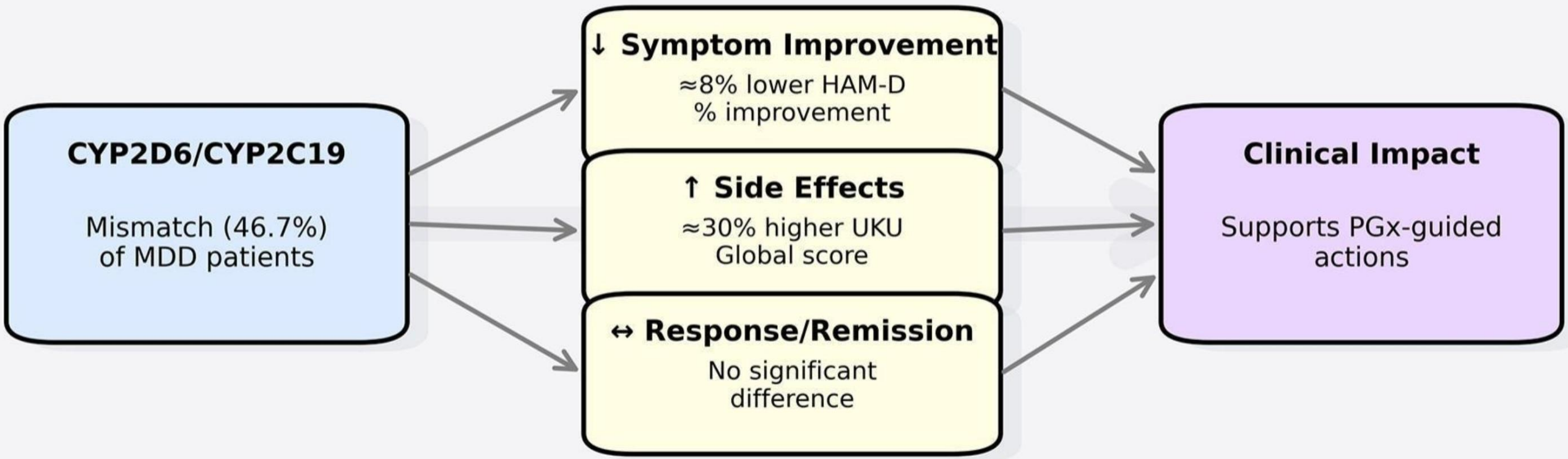
Despite over 30 approved antidepressants, routine care remains **trial-and-error**

One overlooked aspect is the **mismatch scenario**: patients who, despite having known PGx phenotypes, remain on drugs for which their metabolic capacity is sub-optimal—either sub-therapeutic (ultrarapid metaboliser, UM) or supra-therapeutic (poor metaboliser, PM).

Highlights

- Almost half (46.7%) of MDD out-patients received a CYP2D6/CYP2C19 phenotype-drug mismatch.
- Mismatch was linked to a reduction in HAM-D symptom improvement across 12 weeks.
- Patients with mismatch showed ~30% higher UKU global side-effect scores from week 8 onward.
- Results support routine PGx testing and proactive switching of mismatched antidepressants to improve efficacy and safety.

CYP2D6/CYP2C19 Mismatch and Antidepressant Outcomes



Current PSYCHIATRY

Suicide, depression, and CYP2D6: How are they linked?

© JOHN FEDELE/BLEND IMAGES/CORBIS

Shahid Ali, MD
Meharry Medical College
Nashville, TN

Charles D. Mouton, MD
Meharry Medical College
Nashville, TN

Suicide risk might be increased in depressed patients who are ultra-rapid metabolizers

Genetic variations in drug-metabolizing enzymes dramatically affect drug pharmacokinetics and can result in clinically relevant differences in drug efficacy or toxicity. Cytochrome P450 (CYP) enzymes such as CYP2D6 are involved in metabolism of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), which often are a first-line choice for patients with major depressive disorder (MDD).[1,2] CYP2D6 is a highly polymorphic gene with 75 allelic variants (CYP2D6*1 to *75) and >30 additional subvariants.[3] These variants are associated with phenotypes where CYP2D6 activity is increased, reduced, or lost, which can increase the risk of adverse drug reactions, decrease efficacy, and possibly influence a patient's suicide risk.

In this article, we review the pharmacogenetics of CYP2D6 and discuss a possible relationship between CYP2D6 genotype and suicidal events during antidepressant treatment for MDD.

Genetic variations in cytochrome P450 (CYP) 2D6 may increase how quickly a patient metabolizes antidepressants.

Ultra-rapid CYP2D6 metabolizers may be at risk for adverse consequences of untreated depression, including suicide.

CYP2D6 status also may impact a patient's suicide risk through mechanisms other than antidepressant metabolism.

CYP2C9 variants

The *CYP2C9* gene encodes an enzyme that is involved in the metabolism of many drugs, including antidepressants, such as MAOIs, TCAs, and SSRIs.

The CYP2C9*1 variant is associated with **normal enzyme function**

The CYP2C9*2, *5, *8, and *11 variants **reduce** CYP2C9 enzymatic capacity.

The CYP2D9*3, *6, and *13 variants are responsible for the **loss of enzyme function**

Moreover, variants of the CYP2C9 gene have been linked to mental disorders such as depression and psychosis

P-glycoprotein variants

P-glycoprotein, commonly referred to as P-gp, is a **membrane transporter** within the ATP-binding cassette (ABC) transporter family. It is encoded by the *ABCB1* or *MDR1* gene, located on chromosome 7.

Efflux pump, contributing to **drug absorption**, distribution, and elimination.

P-gp has been found in various tissues throughout the body, including the liver, kidneys, intestines, and the **blood-brain barrier**. At the blood-brain barrier, P-gp can limit the entry of some drugs into the brain, which can affect their efficacy.

P-gp has broad substrate specificity, including antidepressants such as escitalopram, fluvoxamine, paroxetine, amitriptyline, and imipramine.

Therefore, **when P-gp is absent or not functioning properly, these drugs can accumulate in the body**, resulting in higher concentrations and potentially an **increased risk of adverse effects**.

However, newer antidepressants (levomilnacipran, vortioxetine, and vilazodone) have been proven as poor P-gp substrates

Several genetic variants of the *MDR1/ABCB1* gene have been associated with altered P-gp activity.

The three most common MDR1/ABCB1 variants, **C3435T (rs1045642), C1236T (rs1128503), and G2677T (rs2032582)**, have been the subject of extensive research.

Genetic variants of the ABCB1 gene, including the **rs2235040 and rs4148739** polymorphisms, may be associated with the onset of response to antidepressant medications rather than the response rate.

Further investigation is necessary to better comprehend the connection between genetic variations and treatment response, as well as to assess its clinical utility.

Review > Clin Pharmacokinet. 2004;43(9):553-76. doi: 10.2165/00003088-200443090-00001.

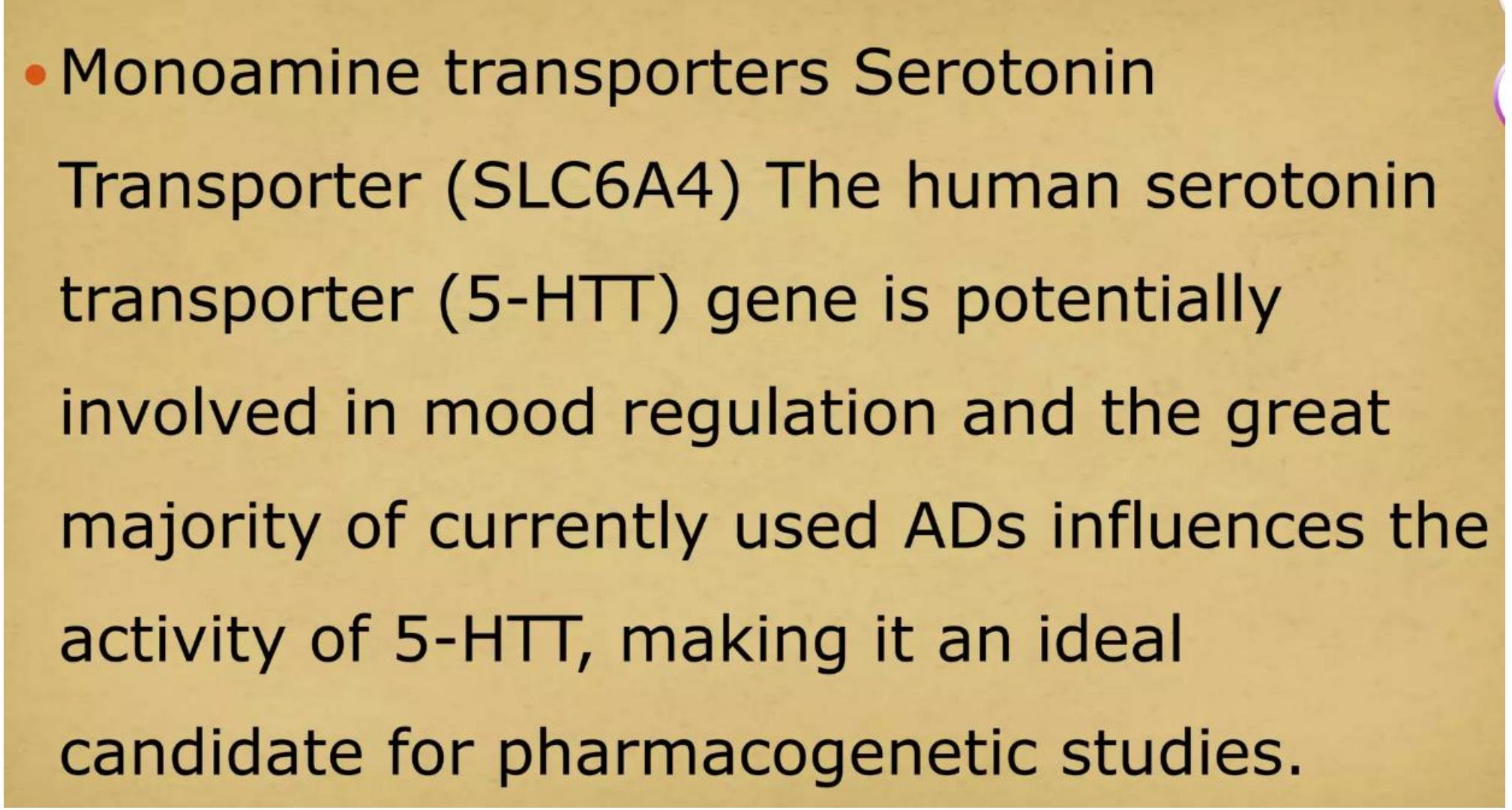
The MDR1 (ABCB1) gene polymorphism and its clinical implications

Ichiro Ieiri [1], Hiroshi Takane, Kenji Otsubo

Affiliations + expand

PMID: 15217301 DOI: 10.2165/00003088-200443090-00001

The clinical relevance of P-glycoprotein depends on the localisation in human tissues (i.e. vectorial or directional movement), the therapeutic index of the substrate drug and the inherent inter- and intra-individual variability.



Several classes of antidepressant drugs, including SSRIs, SNRIs, and TCAs, target **SERT** and inhibit its activity

- A 44-bp insertion/deletion poly-morphism with 2 allelic forms within the serotonin transporter gene promoter regior (5-HTTLPR) that could affect SLC6A4 expression was shown to have functional significance with the long allele (l) associated with two times higher 5-HTT expression in the basal state compared to the s allele according to in vitro studies
- Caucasian subjects report that presence of the s allele is associated with lower response and remission

As a result, carriers of the S allele have been found to have lower serotonin reuptake efficiency, leading to higher serotonin levels.

Therefore, individuals carrying the **S/S** genotype have been shown to have a **poorer response to SSRI treatment** and may experience more side effects compared to those with the L/L (L is long allele) or L/S (S is short allele) genotypes.

Different studies:

- **S/S** genotype resulted in **ineffective fluoxetine** treatment and may have caused exacerbation of depression

- No association between 5-HTTLPR polymorphism and clinical response to escitalopram but higher risk for adverse effects

The **5-HTTLPR polymorphism** may be a **valuable marker** for predicting antidepressant responses and tolerability in individuals with psychiatric disorders.

In particular, genotyping for the 5-HTTLPR variant may help identify patients who are less likely to respond to SSRIs and may benefit from alternative treatment strategies, such as SNRIs or TCAs.

Several studies have reported an association between **the 5-HTTLPR S/S genotype and suicidal behavior**, although **other risk factors**, such as life stressors, psychiatric disorders, and substance use, must be considered.

Article | Open access | Published: 07 May 2025

The interplay between SLC6A4 and HTR1A genetic variants that may lead to antidepressant failure

Sandra Hanna ✉, Mark Faiz, Sanjida Ahmed, Cindy Hsieh, Sara Temkit, Cristina Nunez & Feng Zhou

The Pharmacogenomics Journal **25**, Article number: 13 (2025) | Cite this article

The serotonin transporter (*SLC6A4*) and the serotonin autoreceptor (*HTR1A*) are two of the **most extensively studied genes** in the field of psychiatry, and their variants have been **implicated in antidepressant response**, specifically with selective serotonin reuptake inhibitors (SSRIs) which are widely regarded as the first-line medications for depression and anxiety.

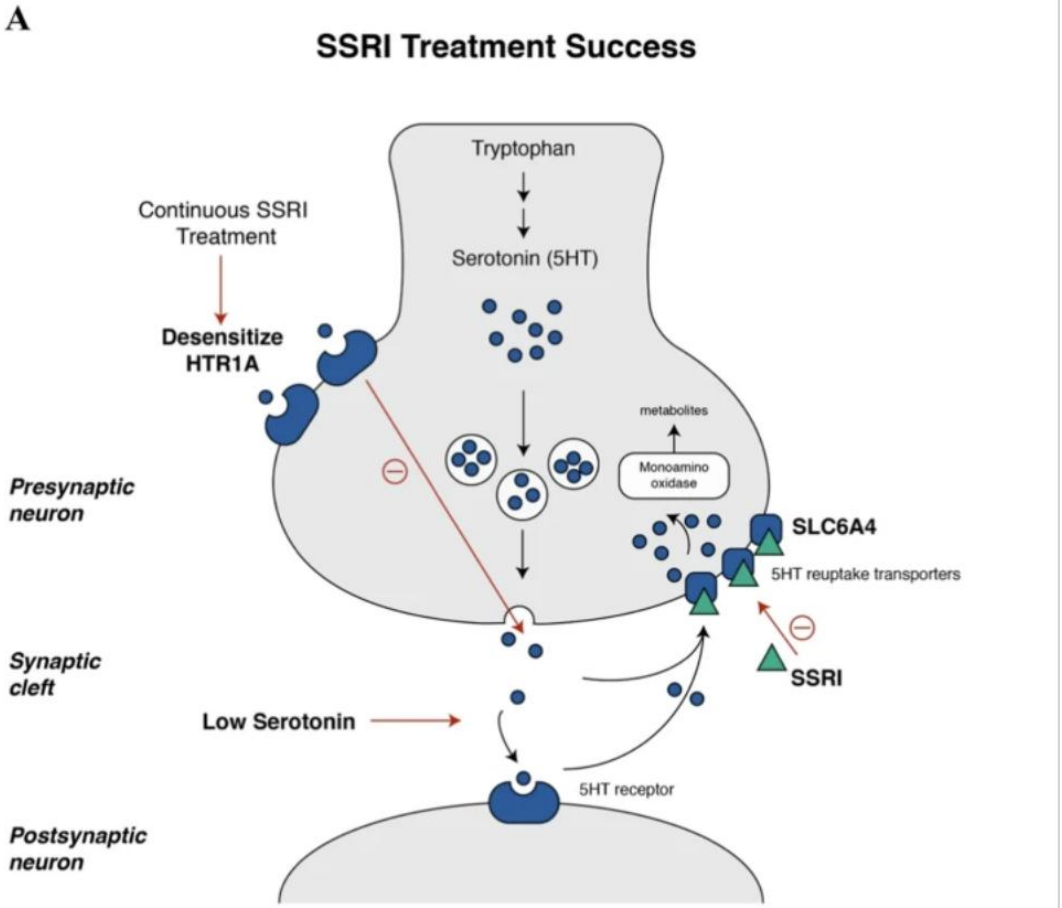
Variants of SLC6A4 and HTR1A have also been studied as risk factors for depression

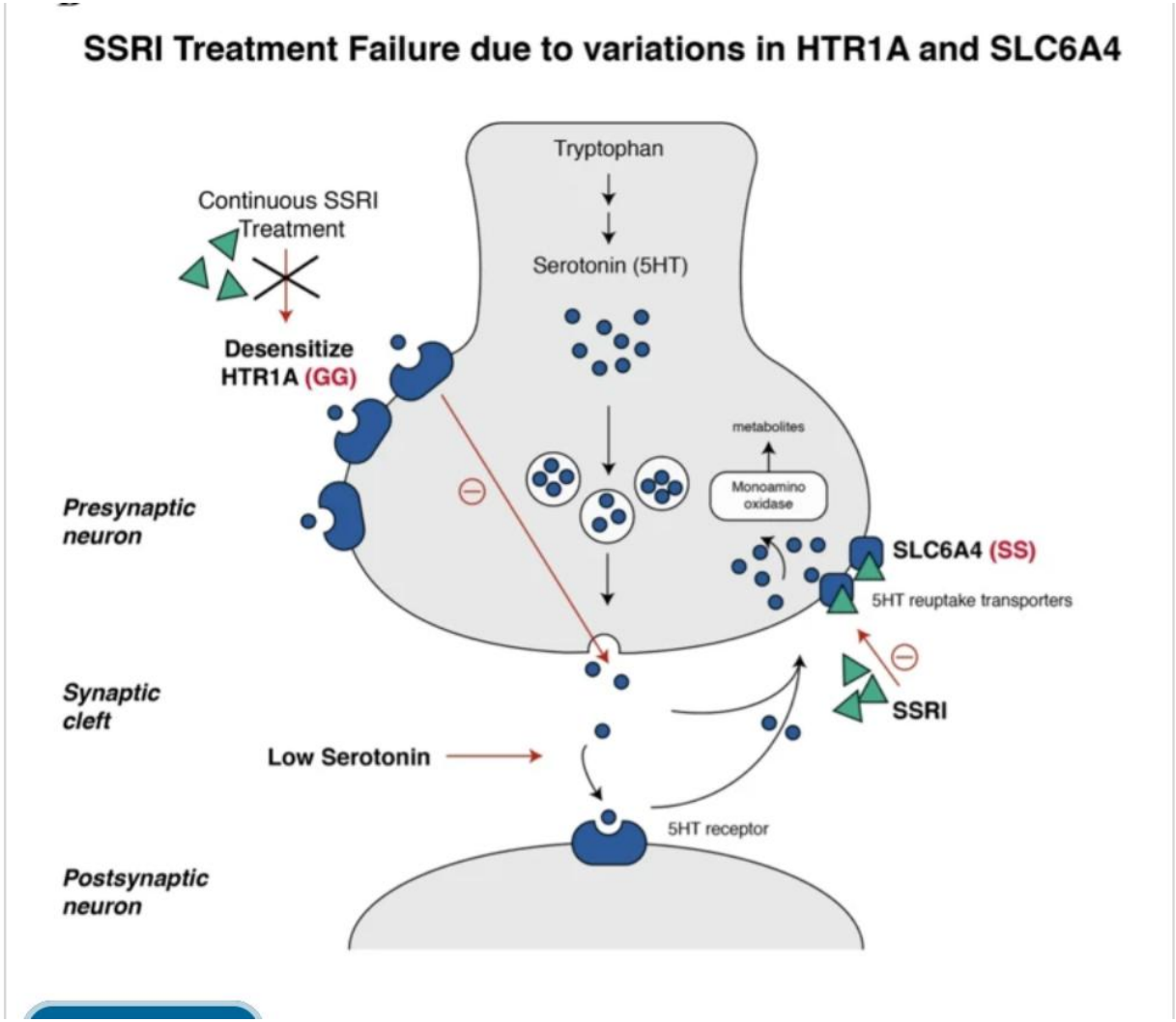
AIM

to investigate **the relationship between all possible serotonin transporter (SLC6A4) and autoreceptor (HTR1A) variant expression combinations** that may have contributed to the **therapeutic failure** of an SSRI and subsequent disability.

The **G allele** of the HTR1A gene (rs6295, C-1019G) works by **increasing** presynaptic 5-HT1A receptor expression, causing higher receptor density and lower serotonin levels due to increased auto-inhibitory feedback.

Fig. 1: Interactive effects of HTR1A rs6295 and SLC6A4 polymorphisms on SSRI treatment.





We therefore propose that **the two genes (*SLC6A4* and *HTR1A*) ought to be studied together to determine SSRI efficacy**.

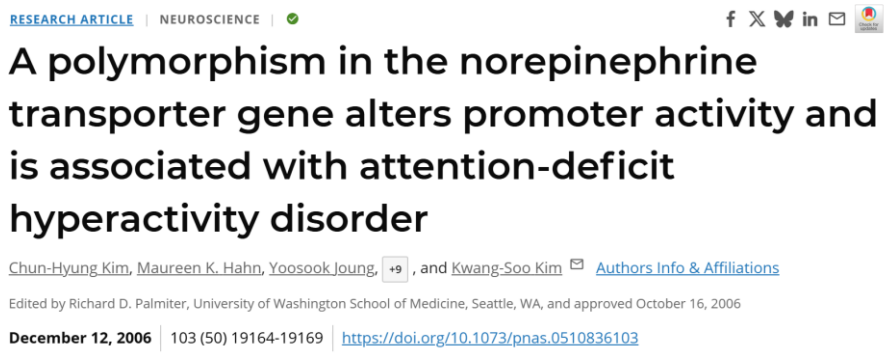
Most of the patients (74%) who have claimed disability because of failed treatment of depressive or anxious disorders and who were referred to PPI for a pharmacogenomic test have genetic profiles that predispose them to therapeutic failure of first-line antidepressant medications (SSRIs).

→ **the S allele of *SLC6A4* and G allele of *HTR1A* are overrepresented**

Noradrenalin Transporter (SLC6A2)

- According to the results of a recent GWAS study cer-tain genetic variations of the noradrenalin transporter may be associated with the risk of MDD. In addition, the noradrenalin transporter is the principal site of action of some ADs

The norepinephrine transporter (**NET**) is a protein encoded by the *SLC6A2* gene and plays an important role in the reuptake of norepinephrine (NE).



RESEARCH ARTICLE | NEUROSCIENCE |

A polymorphism in the norepinephrine transporter gene alters promoter activity and is associated with attention-deficit hyperactivity disorder

Chun-Hyung Kim, Maureen K. Hahn, Yoosook Joung, +9, and Kwang-Soo Kim Authors Info & Affiliations

Edited by Richard D. Palmiter, University of Washington School of Medicine, Seattle, WA, and approved October 16, 2006

December 12, 2006 | 103 (50) 19164-19169 | https://doi.org/10.1073/pnas.0510836103

Significant association between the −3081(A/T) polymorphism and attention-deficit hyperactivity disorder (ADHD), suggesting that anomalous transcription factor-based repression of *SLC6A2* may **increase risk for the development of attention-deficit hyperactivity disorder and other neuropsychiatric diseases.**

TCAs, such as **desipramine and imipramine**, work by inhibiting the reuptake of NE by the NET, which increases the levels of NE in the synapse and enhances its effects on target neurons.

Although antidepressants, such as SSRIs, have largely replaced TCAs, they are still used in some cases where other treatments have been ineffective.

Several genetic variants have been identified in the human SLC6A2 gene, which have functional consequences and can affect the efficacy of antidepressant drugs → **the role of SLC6A2 variants in antidepressant responses is still being studied**, current evidence suggests that these associations are complex and not fully understood.

Neuroscience Applied
Volume 2, 2023, 101016

Short Communication

Polymorphisms in the adrenergic neurotransmission pathway impact antidepressant response in depressed patients

Taichi Ochi [a], Natalya M. Vyalova [b], Innokentiy S. Losenkov [b], Diana Z. Paderina [b], Ivan V. Pozhidaev [b], Anton J.M. Loonen [a], German G. Simutkin [b], Nikolay A. Bokhan [b c d], Bob Wilffert [a e 1], Svetlana A. Ivanova [b d f]

Show more

- *SLC6A2* polymorphisms (NET) associated with the varied response to antidepressants.

Dopamine Transporter (SLC6A3)

- It is assumed that dopaminergic mechanisms play an important role in AD drug action, since AD drugs, in particular dopamine/norepinephrine reuptake inhibitor bupropion and specific members of SSRIs (mainly sertraline) modulate activity of the dopamine transporter.
- A 40-base pair VNTR polymorphism in the SLC6A3 gene, encoding for the dopamine transporter (DAT) has been associated with expression levels of the transporter.

These polymorphisms, notably the 9-repeat (9R) and 10-repeat (10R) alleles, significantly influence **DAT** **expression and dopamine clearance**, linking them to ADHD, Parkinson's disease, and stimulant response

The *SLC6A3* gene has been identified with at least **502 variations**.

Some studies have suggested that specific SLC6A3 polymorphisms **may influence the response to antidepressant therapy**

SLC6A3 polymorphism increased the risk of a poorer and slower response to various antidepressants in individuals

The relationship between SLC6A3 polymorphisms and antidepressant responses is yet to be thoroughly researched

Review > Biomedicines. 2023 Aug 15;11(8):2270. doi: 10.3390/biomedicines11082270.

The *3'UTR VNTR SLC6A3* Genetic Variant and Major Depressive Disorder: A Systematic Review

Bruna Rodrigues Gontijo [1], Isabella Possatti [1], Caroline Ferreira Fratelli [1], Alexandre Sampaio Rodrigues Pereira [1], Larissa Sousa Silva Bonasser [2], Calliandra Maria de Souza Silva [1], Izabel Cristina Rodrigues da Silva [1]

Affiliations + expand

PMID: 37626766 PMCID: PMC10452352 DOI: 10.3390/biomedicines11082270

Abstract

This systematic review aims to verify the *SLC6A3 (DAT1) 3'UTR VNTR (rs28363170)* gene variant's SS (9R/9R) genotype and S (9R) allele frequency fluctuation and its influence on the modulation of pharmacotherapy in MDD.

Studies have shown an association between the **SS (9R/9R) genotypic and S (9R) allelic** presence with the **risk of developing MDD**, in addition to influencing the **decrease in response to antidepressant therapy.**

Disagreements were observed between other studies. For this reason, further studies with the SLC6A3 3'UTR VNTR (rs28363170) variant in different populations are necessary to understand this polymorphism's role in the onset of this disease.

Monoamine Metabolic Enzymes

- Tryptophan hydroxylase
- The tryptophan hydroxylase (TPH) gene encoding the rate-limiting enzyme in serotonin synthesis has been studied intensively in psychiatric disorders, yielding mixed results.

Tryptophan hydroxylase (TPH) is an enzyme that catalyzes the conversion of the amino acid tryptophan to 5-hydroxytryptophan, which is the first step in the **synthesis** of serotonin, a neurotransmitter involved in the regulation of mood, appetite, sleep, and stress response

There are two isoforms of the TPH enzyme, **TPH1 and TPH2**, encoded by separate genes.

TPH1 is primarily expressed in peripheral tissues, such as the pineal gland, skin, and gut, whereas **TPH2** is mainly expressed in neurons in the central nervous system (CNS).

The two isoforms have similar enzymatic activities but differ in regulation, tissue distribution, and developmental expression patterns

Key variants, **notably in TPH2** (e.g., rs4570625, rs4290270) and TPH1 (e.g., A218C, rs4537731), are **strongly associated with major depressive disorder** (MDD), suicidal behavior, anxiety, and irritable bowel syndrome (IBS)

However, several studies have demonstrated controversial results regarding TPH polymorphisms and response to SSRIs

ORIGINAL RESEARCH article

Front. Neurosci., 15 November 2018

Sec. Brain Imaging Methods

Volume 12 - 2018 | https://doi.org/10.3389/fnins.2018.00827

TPH-2 Gene Polymorphism in Major Depressive Disorder Patients With Early-Wakening Symptom

These findings suggested that the TPH-2 gene variant, rs4290270, affected the circadian regulating function of SCN (suprachiasmatic nuclei)

rs4290270 could potentially serve as a reliable biomarker to identify MDD patients with early wakening symptom.

Review article ● Full text access Get rights and content ↗

Meta-analysis of association between TPH2 single nucleotide poiymorphism and depression

Zhang-Lin Liu [1] ✉, Xin-Qiang Wang [1] ✉, Ming-fan Liu ✉, Bao-juan Ye ✉ Show more

View PDF Download full issue Cite Add to Mendeley Share 10.1016/j.neubiorev.2021.104517 ↗

We reviewed **40 research papers** that included data on TPH2 gene single nucleotide polymorphisms (SNPs) from **5766 patients with depression and 5988 healthy subjects**.

The analysis showed an association between polymorphisms in the TPH2 gene and depression

rs4570625, rs17110747, rs120074175, rs4290270, rs120074175, and rs4290270 may be **significantly associated with depression**

rs11178997 (A/A genotype) may be a significant risk factor for depression

Catechol-O-Methyltransferase (COMT)

- The COMT enzyme is responsible for the inactiva-tion of various catecholamines including dopamine, adrenalin and noradrenalin.
- The COMT gene has several allelic variants, including the most extensively studied rs4680 variant.
- A functional G to A SNP at codon 158 leading to a Val to Met substitution was identified contributing to a high activity Val/Val, intermediate activity Val/Met, low activity in Met/Met genotype

The *COMT* gene has several polymorphisms, and the most extensively studied is the **rs4680 polymorphism**, also known as Val158Met

This SNP causes the substitution of valine (Val) for methionine (Met) at position 158 in the COMT enzyme.

The **Val allele is associated with higher COMT activity**, whereas the **Met allele leads to lower activity**

The COMT Val158Met polymorphism has been implicated in various psychiatric disorders, including depression, anxiety, and schizophrenia

COMT Val158Met polymorphism affect the response the to SSRIs such as **fluoxetine and paroxetine**

Val/Met genotype significantly affected the response to fluvoxamine

The effects of the COMT genotype on antidepressant responses may depend on **other factors**, such as the type of medication, severity and duration of depression, and other genetic and environmental factors

Review

The role of COMT gene variants in depression: Bridging neuropsychological, behavioral and clinical phenotypes

Niki Antypa [a b], Antonio Drago [c], Alessandro Serretti [a] Show more

10.1016/j.neubiorev.2013.06.006 ↗

Highlights

- We examined the role of COMT genetic variations on depressive (endo)phenotypes.
- COMT genetic effects are discernible on brain systems of emotional processing.
- The val158met polymorphism may influence antidepressant response.
- COMT genetic variation is not directly related to depression diagnosis or severity.
- Gender and stress are important modulators of COMT genetic effects.

Monoamine Oxidase A (MAO-A)

- MAO-A is one of the enzymes responsible for the degradation of monoamine neurotransmitters. One polymorphism in the promoter region of the MAO-A gene consisting of a repetitive sequence (VNTR) has been linked to variations in the biological activity and consequentially serotonin concentrations.
- Variants with 3.5 or 4 copies of the repeat sequence ("MAO-A High") are expressed 2-10 times more efficiently than those with 2, 3 or 5 copies of the repeat

There are two types of MAOs, MAO-A and MAO-B, which are encoded by separate genes.

MAO-A and MAO-B are found in the CNS, particularly in neurons and astroglia.

MAO-A is primarily responsible for the metabolism of several important monoamine neurotransmitters, including serotonin, norepinephrine, and dopamine.

These neurotransmitters play a crucial role in the regulation of mood, behavior, and cognition

MAO-A variants have been linked to an increased risk of developing psychiatric disorders. However, **the relationship between the MAO-A gene variants and psychiatric disorders remains unclear.**

Polymorphisms in MAO genes have also been studied for **their potential role in response to antidepressant medications**. Some studies have suggested that certain genetic variants in MAO genes **may affect the metabolism of antidepressants**, potentially leading to differences in drug efficacy and side effects.

Individuals with a **specific variant of the MAO-A gene** had a better response to fluvoxamine compared to those without this variant. In addition, a recent study reported that the **MAO-A rs979605** polymorphism might **modulate the response to antidepressant therapy in a sex-specific manner.**

Research article ● Full text access Get rights and content ↗

Monoamine oxidase A variant influences antidepressant treatment response in female patients with Major Depression

Katharina Domschke [a], Christa Hohoff [a], Lena S. Mortensen [a], Tilmann Roehrs [a], Jürgen Deckert [b], Volker Arolt [a], Bernhard T. Baune [a c]
Show more

The present results suggest that **high-activity MAO-A genotypes** possibly by consecutively **decreased serotonin and/or norepinephrine** availability **negatively influence antidepressant treatment** response during the first six weeks of pharmacological treatment in female patients with Major Depression.

CPIC Guideline for CYP2D6, CYP2C19, CYP2B6, SLC6A4, HTR2A and Serotonin Reuptake Inhibitor Antidepressants

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6, CYP2C19, CYP2B6, SLC6A4, and HTR2A Genotypes and Serotonin Reuptake Inhibitor Antidepressants.

The 2023 guideline is a major update to the original "Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors" that was published in 2015. More genes and drugs were evaluated and prescribing recommendations were expanded.

Drugs and Genes

✓ With Actionable Recommendations

For more details about CPIC guidance, including specific drug recommendations by genotype or phenotype, use the links below.

citalopram and CYP2C19
escitalopram and CYP2C19
fluvoxamine and CYP2D6
paroxetine and CYP2D6
sertraline, CYP2B6 and CYP2C19
venlafaxine and CYP2D6
vortioxetine and CYP2D6

Download Files

Download Publication

Supplement

37032427-supplement.pdf

Allele Definition Table

CYP2B6 CYP2C19
CYP2D6

Allele Functionality Table

CYP2B6 CYP2C19
CYP2D6

https://www.clinpgx.org/guideline/PA166251452

🚫 Without Actionable Recommendations

The following genes and drugs were evaluated by CPIC but were determined not to have an actionable recommendation. For more details, use the links below.

citalopram and HTR2A
citalopram and SLC6A4
desvenlafaxine and HTR2A
desvenlafaxine and SLC6A4
duloxetine and CYP2D6
duloxetine and HTR2A
duloxetine and SLC6A4
escitalopram and HTR2A
escitalopram and SLC6A4
fluoxetine and CYP2D6
fluoxetine and HTR2A
fluoxetine and SLC6A4
fluvoxamine and HTR2A
fluvoxamine and SLC6A4
levomilnacipran and HTR2A
levomilnacipran and SLC6A4
milnacipran and HTR2A
milnacipran and SLC6A4
paroxetine and HTR2A
paroxetine and SLC6A4
sertraline and HTR2A
sertraline and SLC6A4
venlafaxine and HTR2A
venlafaxine and SLC6A4
vilazodone and HTR2A
vilazodone and SLC6A4
vortioxetine and HTR2A
vortioxetine and SLC6A4

PHARMACOGENETICS OF ANTIPSYCHOATICS

- Since chlorpromazine was first introduced into clinical psychiatry, various kinds of antipsychotics have been developed and used for schizophrenia.
- Clinicians, however, still have considerable difficulty in choosing an appropriate antipsychotic for certain patients due to the inter-individual diversities of drug response.

Pharmacokinetics of antipsychotics

- Most antipsychotics are extensively metabolized by cytochrome (CYP) P450s that are members of a super-family of oxidative enzymes and that constitute a major system for the oxida-tive metabolism of therapeutic substances.

- The CYP2D6 has been most extensively investigated in the field of psychiatry, since this enzyme is involved in the metabolism of many antipsychotics and has many genetic polymorphisms that influence the function of the enzyme.

- There are more than 70 variant alleles at the CYP2D6 gene locus, including the two most common variants, CYP2D6*4 and CYP2D6*45, encoding non-functional products.1 Other variants that reduce activity, alter substrate specificity or increase activity have also been described

- Compared with efficient metabolizers (EM), poor metabolizers (PM) show no or reduced CYP2D6 activity bypolymorphisms resulting in potentially increased concentrations of metabolized drugs.

- PMs have higher plasma concentrations of and suffer more adverse effects from antipsychotics. The incidence of the acute side effects of these drugs, including postural hypotension, excess sedation, or extrapyramidal symptoms, is disproportionately in PMs.

- On the other hand, it is not clear whether the development of chronic side effects such as tardive dyskinesia is associated with a reduced metabolizing capacity of CYP2D6.

Review > Pharmacogenomics. 2007 Nov;8(11):1597-608. doi: 10.2217/14622416.8.11.1597.

CYP2D6 polymorphism: implications for antipsychotic drug response, schizophrenia and personality traits

Pedro Dorado [1], Eva M Peñas-Lledó, Adrián Llerena

Affiliations + expand

PMID: 18034624 DOI: 10.2217/14622416.8.11.1597

Abstract

The CYP2D6 gene is highly polymorphic, causing absent (poor metabolizers), decreased, normal or increased enzyme activity (extensive and ultrarapid metabolizers). The genetic polymorphism of the CYP2D6 influences plasma concentration of a wide variety of drugs metabolized in the liver by the cytochrome P450 (CYP) 2D6 enzyme, including antipsychotic drugs used for schizophrenia treatment. Additionally, CYP2D6 is involved in the metabolism of endogenous substrates in the brain, and reported to be located in regions such as the cortex, hippocampus and cerebellum, which are impaired in schizophrenia. Moreover, recently we have found that CYP2D6 poor metabolizers are under-represented in a case-control association study of schizophrenia. Furthermore, null CYP2D6 activity in healthy volunteers is associated with personality characteristics of social cognitive anxiety, which may bear some resemblance to milder forms of psychotic-like symptoms. In keeping with this, CYP2D6 may influence, not only variability to drug response, but also vulnerability to disease in schizophrenia patients.

Furthermore, **null CYP2D6 activity** in healthy volunteers is **associated with personality characteristics of social cognitive anxiety,** which may bear some resemblance to milder forms of psychotic-like symptoms.

In keeping with this, CYP2D6 may influence, not only variability to drug response, but also vulnerability to disease in schizophrenia patients.

RESEARCH ARTICLE · Volume 10, Issue 7, e28832, April 15, 2024 · *Open Access*

Effects of *CYP2D6* gene polymorphism on plasma concentration and therapeutic effect of olanzapine

Ye Yang [a] · Wenqing Liu [b] · Renrong Wu [c]

Affiliations & Notes · Article Info

Abstract

This study aimed to evaluate the relationship between gene polymorphisms of metabolic enzymes, particularly the *CYP2D6* gene, and the plasma concentration of olanzapine, as well as treatment response in patients with chronic schizophrenia. We recruited olanzapine-treated patients and examined their plasma olanzapine levels. Additionally, a common mutation site within each of the nine exons of the full-length *CYP2D6* sequence was assayed. The Positive and Negative Syndrome Scale, Brief Psychiatric Rating Scale, and Overall Clinical Impression were used to assess schizophrenic symptoms, whereas the Barnes Akathisia Scale and Extrapyramidal Symptom Rating Scale were used to evaluate adverse effects. The results showed no significant differences in plasma olanzapine concentrations, treatment response, or the occurrence of adverse effects among different *CYP2D6* genotypes. However, an association between olanzapine concentrations and improvement in clinical symptoms and adverse reactions was observed. In conclusion, the CYP2D6 genotype did not significantly impact plasma olanzapine concentrations, treatment response, or the occurrence of adverse effects.

Show Outline

AIM:

to evaluate the **relationship between** gene polymorphisms of metabolic enzymes, particularly the ***CYP2D6*** gene, **and the plasma concentration of olanzapine**, **as well as treatment response in patients** with chronic schizophrenia.

RESULTS:

showed **no significant differences** in plasma olanzapine concentrations, treatment response, or the occurrence of adverse effects among different *CYP2D6* genotypes

CONCLUSION:

the CYP2D6 genotype did not significantly impact plasma olanzapine concentrations, treatment response, or the occurrence of adverse effects.

Why???? It is mainly metabolized by CYP1A2.

Vol. 40. Issue 1.
(January - March 2026)

Export refe

Outline

Abstract

Keywords

Introduction

Methods

Results

DOI: 10.1016/j.ejpsy.2025.100338

Full text access

Heterogeneity in the association between CYP2D6 genotype and antipsychotic-induced extrapyramidal symptoms: A systematic review

Antonina Luca[a], Maria Luca[b], Paolo Olgiati[a,c], Alessandro Serretti[a,c]

[a] Department of Medicine and Surgery, Kore University of Enna, Italy
[b] Centre for Addiction, Adrano-Bronte, Italy
[c] Oasi Research Institute-IRCCS, Troina, Italy

Aim of the present review was to critically summarize **the evidence linking CYP2D6 genotype with antipsychotic-induced EPS (extra-pyramidal symptoms)**.

Conclusion

Some studies summarized in the present review supported the role of CYP2D6 genotype in the occurrence of EPS in patients treated with antipsychotics, **particularly with high-potency D_2 antagonists**.

Pharmgenomics Pers Med. 2016 Dec 1;9:131–147. doi: 10.2147/PGPM.S107772

CYP2D6 polymorphisms and their influence on risperidone treatment

Apichaya Puangpetch [1], Natchaya Vanwong [1], Nopphadol Nuntamool [2], Yaowaluck Hongkaew [1], Monpat Chamnanphon [1], Chonlaphat Sukasem [1,✉]

Author information · Article notes · Copyright and License information

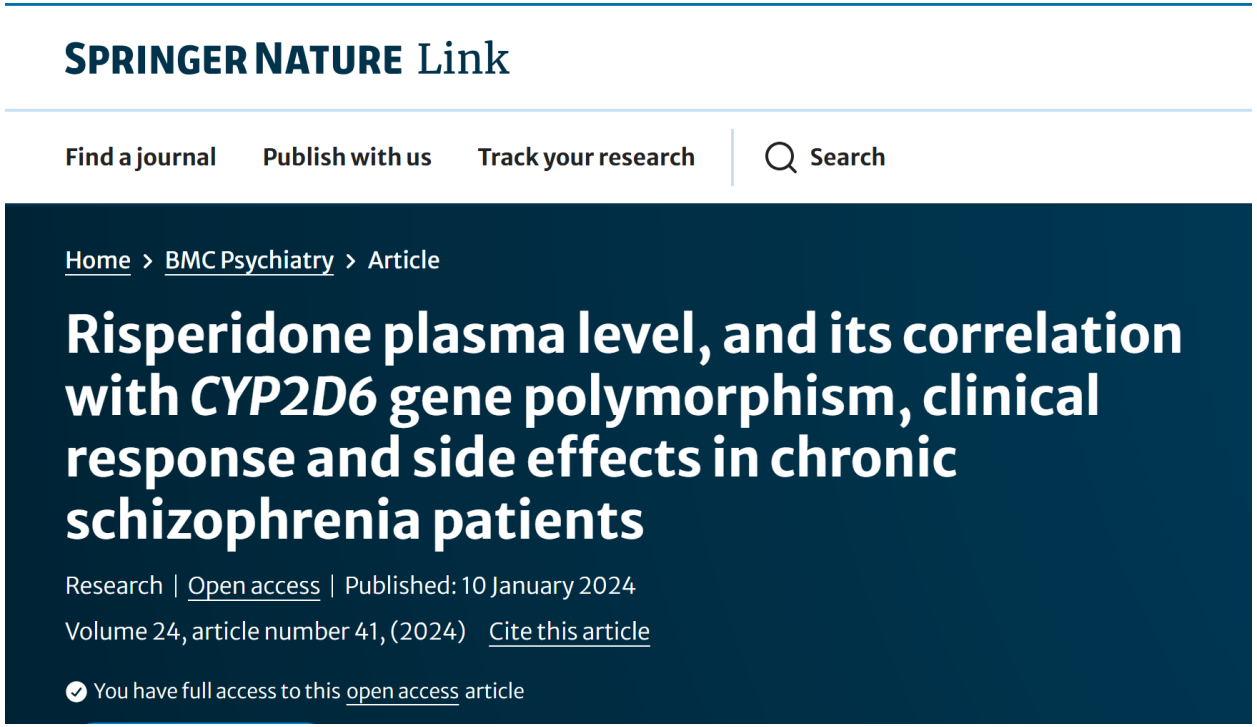
PMCID: PMC5138038 PMID: 27942231

CYP2D6 **poor metabolizer showed more serious adverse events** such as weight gain and prolactin than other predicted phenotype groups

Both the CYP2D6 genotyping and therapeutic drug monitoring are the important steps to complement the genetic-based risperidone treatment

The effective responses in risperidone treatment depend on the CYP2D6 polymorphisms.

Several studies suggested that ***CYP2D6*** **polymorphisms were associated with plasma concentration of risperidone**, 9-hydroxyrisperidone, and active moiety **but did not impact on clinical outcomes**.



To explore the characteristics of **risperidone** serum concentration and its main influencing factors, the *CYP2D6* polymorphism, as well as the relationship
between plasma drug concentration and efficacy and adverse reactions on chronic schizophrenia patients.

The results suggest that **the plasma concentrations** of risperidone,
9-hydroxyrisperidone and active moiety **have great inter- and intraindividual variations**, and are **associated**
with the *CYP2D6* polymorphism.

Besides, it related to changes in serum prolactin in patients diagnosed with chronic schizophrenia. But it seems to have **no correlation with clinical response**.

These findings should be replicated with a large sample of subjects.

Population Study Article | Published: 19 January 2019

CYP2D6 genotype and adverse events to risperidone in children and adolescents

Kazeem A. Oshikoya, Katelyn M. Neely, Robert J. Carroll, Ida T. Aka, Angela C. Maxwell-Horn, Dan M. Roden & Sara L. Van Driest

Pediatric Research **85**, 602–606 (2019) | Cite this article

This study assessed the **association between CYP2D6 metabolizer status and risk for risperidone AEs in children.**

In multivariate analysis adjusting for age, sex, race, and initial dose, **poor/intermediate metabolizers had increased AE risk**.

Pre-prescription genotyping could identify this high-risk subset for an alternate therapy, risperidone dose reduction, and/or increased monitoring for AEs.

- All receptor and transporter genes for neurotransmitters as well as genes located down-stream of the intracellular signaling pathways can be considered candidate genes for the pharmacodynamics of antipsychotics.

- genetic polymorphisms in serotonin (5-HT) and dopamine (DA) systems have been extensively investigated in the pharmacodynamics of antipsychotics

DA system

- The first candidate gene examined with regard to clozapine response was the DA4 receptor gene (DRD4) because in addition to its high affinity for clozapine, the DA4 receptor is abundant in the prefrontal cortex, (a brain region thought to be related to the cognitive dysfunction of schizophrenia), and the DRD4 gene itself is highly polymorphic.

DA system

- Among polymorphisms in the DRD4, the 48 bp variable number of tandem repeats (VNTR) has been the most extensively investigated, since the VNTR was shown an in vitro study to influence the sodium chloride sensitivity of clozapine-binding and inhibition of c-AMP synthesis.

This **variation** dictates the number of amino acid sequences in the receptor's third cytoplasmic loop, which **alters how the receptor functions and interacts with drugs**.

The 48-bp Repeat (Exon III): This is the most famous DRD4 polymorphism.
In vitro studies show that these structural variants have different binding affinities and sensitivities to medications, directly impacting how patients respond to antipsychotics.

The 120-bp Repeat (Exon I): Found in the promoter region studies have shown that patients with specific 120-bp allele genotypes (such as the 1-repeat allele) coupled with other genetic markers (like COMT gene variations) **show a significantly better clinical response** to clozapine.

Other Variants: Single Nucleotide Polymorphisms (SNPs) like the -521 C>T promoter variant are also associated with \(D_{4}\) expression and clozapine's clinical efficacy

Psychopharmacology (Berl). 1999 Jan;141(1):6-10. doi: 10.1007/s002130050799.

Polymorphisms of the dopamine D4 receptor and response to antipsychotic drugs

B M Cohen [1], D J Ennulat, F Centorrino, S Matthysse, H Konieczna, H M Chu, S Cherkerzian

Affiliations + expand

PMID: 9952058 DOI: 10.1007/s002130050799

Clozapine, an atypical antipsychotic used primarily for treatment-resistant schizophrenia, is unique because it binds to the D4 receptor with an affinity up to 10 times higher than it does to the standard D2 receptor.

Abstract

The dopamine D4 receptor may be a site through which the clinical effects of antipsychotic drugs are mediated. Polymorphisms of a 48 base pair repeat in the third exon of the DRD4 gene code for different length segments in the third intracytoplasmic loop of the D4 receptor. The most common long (seven repeat) form of the D4 receptor has been shown in both physiologic and pharmacologic experiments to respond differently to dopamine agonists and antagonists than do shorter forms of D4. Thus, variants of D4 may partly determine patient response to antipsychotic drugs and, in particular, response to typical neuroleptics, which have a relatively low affinity for the D4 receptor, as compared to clozapine, which has a relatively high affinity for D4. DRD4 polymorphisms in the third intron were characterized in 28 patients with chronic psychosis who responded well to typical neuroleptics, 32 patients who responded well to clozapine, and 57 healthy comparison subjects. Patients responding to typical neuroleptics carried the allele for the long (seven repeat) form of the D4 receptor (allele frequency 8.9%) less frequently than patients responding to clozapine (allele frequency 23.4%, P = 0.046) or healthy comparison subjects (allele frequency 26.3%, P = 0.004). The results of this study suggest that inherited variants of D4 may explain some of the interindividual variation seen in patient response to different classes of antipsychotic medication.

Patients carrying the allele for the long form less respond to typical neuroleptics but well respond to clozapine

The DA3 receptor

- The DA3 receptor, which shares homologies with both the DA4 and DA2 receptors, has generated interest, since the DA3 receptor gene (DRDA3) has a known functional polymorphism,Ser9Gly, that influences dopamine binding. However, the association between the Ser9Gly and clozapine response remains controversial.

The DA2 receptor

The DA2 receptor is a major site of the action of conventional antipsychotics such as chlorpromazine and haloperidol, and of some atypical antipsychotics such as risperidone. One functional polymorphism (-141 Ins/Del) in the promoter region, as well as missense variants including Ser311Cer and an intronic variant (Taq 1 A), have been identified in the DA2 receptor gene (DRD2).

▸ Am J Psychiatry. Author manuscript; available in PMC: 2010 Jul 3.

Published in final edited form as: Am J Psychiatry. 2010 Mar 1;167(7):763–772. doi: 10.1176/appi.ajp.2009.09040598

Dopamine D2 receptor genetic variation and clinical response to antipsychotic drug treatment: A meta-analysis

Jian-Ping Zhang [1], Todd Lencz [1], Anil K Malhotra [1]

▸ Author information ▸ Article notes ▸ Copyright and License information

PMCID: PMC2896457 NIHMSID: NIHMS182318 PMID: 20194480

The first meta-analysis **to examine the relationship between *DRD2* polymorphisms and antipsychotic drug response.**

DRD2 genetic variation is associated with clinical response to antipsychotic drug treatment. This data may provide proof-of-principle for pharmacogenetic studies in schizophrenia.

5-HT system

- The 5-HT receptor genes have been regarded as good candidates for pharmacodynamic stud-ies of antipsychotics, since 5-HT mediated mechanisms seem crucial to atypical antipsychotic drug action, including that of clozapine.

- An association between the silent polymorphism 102T/C in the 5-HT2A receptor gene (HTR2A) and clozapine has been reported.

- Hys452Tyr12 was shown to influence the intracellular signal transduction of the 5-HT2A receptor, as measured by Ca2+ mobilization induced by 5-HT stimulation.

› Mol Psychiatry. 1998 Jan;3(1):61-6. doi: 10.1038/sj.mp.4000348.

Evidence for association between polymorphisms in the promoter and coding regions of the 5-HT2A receptor gene and response to clozapine

M J Arranz [1], J Munro, M J Owen, G Spurlock, P C Sham, J Zhao, G Kirov, D A Collier, R W Kerwin

Affiliations + expand

PMID: 9491814 DOI: 10.1038/sj.mp.4000348

5-HT2A His452Tyr (rs6313): This missense mutation (histidine-to-tyrosine substitution) is **strongly associated with treatment resistance**. Patients carrying the Tyr452 variant show a significantly reduced clinical response to clozapine, as the receptor alteration diminishes the drug's ability to trigger downstream signaling pathways

5-HT2A 102T/C (rs6315): This silent genetic variation in the coding region has been the subject of extensive pharmacogenetic research. Initial meta-analyses indicated that the C102 allele and C102/C102 genotype are more frequently observed in **patients who respond poorly to clozapine**, although some studies report mixed or statistically insignificant associations across diverse ethnic populations

- In addition to the 5-HT2A receptor, other 5-HT receptors, such as 5-HT 2C and 5-HT 6, have also been investigated in psychopharmacognetic studies because atypical antipsychotics also have high affinity for these receptors.

▸ J Pers Med. 2021 Mar 5;11(3):181. doi: 10.3390/jpm11030181

Genetic Polymorphisms of *5-HT* Receptors and Antipsychotic-Induced Metabolic Dysfunction in Patients with Schizophrenia

Diana Z Paderina [1], Anastasiia S Boiko [1], Ivan V Pozhidaev [1], Anna V Bocharova [2], Irina A Mednova [1], Olga Yu Fedorenko [1], Elena G Kornetova [1,3], Anton JM Loonen [4,*], Arkadiy V Semke [1], Nikolay A Bokhan [1,3], Svetlana A Ivanova [1,3]

Editor: Tomiki Sumiyoshi

These polymorphisms influence adipogenesis (fat cell development) and are frequently studied in relation to obesity, metabolic syndrome, and medication-induced metabolic side effects

Open Access Article

DRD2, DRD3, and HTR2A Single-Nucleotide Polymorphisms Involvement in High Treatment Resistance to Atypical Antipsychotic Drugs

by Antonio Del Casale [1,2,†], Maurizio Simmaco [3,4,†], Martina Nicole Modesti [3], Clarissa Zocchi [3], Jan Francesco Arena [3], Irene Bilotta [3], Alessandro Alcibiade [3], Giuseppe Sarli [3], Lorenzo Cutillo [3], Giulia Antonelli [3], Enrico La Spina [3], Ottavia De Luca [3,4], Robert Preissner [5], Marina Borro [3,4], Giovanna Gentile [3,4], Paolo Girardi [1,*] and Maurizio Pompili [2,3]

[1] Department of Dynamic and Clinical Psychology and Health Studies, Faculty of Medicine and Psychology, Sapienza University of Rome, 00185 Rome, Italy
[2] Unit of Psychiatry, 'Sant'Andrea' University Hospital, 00189 Rome, Italy
[3] Department of Neuroscience, Mental Health and Sensory Organs (NESMOS), Faculty of Medicine and Psychology, Sapienza University of Rome, 00185 Rome, Italy
[4] Unit of Laboratory and Advanced Molecular Diagnostics, 'Sant'Andrea' University Hospital, 00189 Rome, Italy
[5] Structural Bioinformatics Group, Institute for Physiology, Charité—University Medicine Berlin, 10115 Berlin, Germany
* Author to whom correspondence should be addressed.
† These authors contributed equally to this work.

Biomedicines **2023**, *11*(7), 2088; **https://doi.org/10.3390/biomedicines11072088**

Submission received: 25 March 2023 / Revised: 17 July 2023 / Accepted: 21 July 2023 / Published: 24 July 2023

The objective of this study was to investigate the ***DRD2* rs1800497, rs1799732, rs1801028, *DRD3* rs6280, and *HTR2A* rs6314, rs7997012, and rs6311** single-nucleotide polymorphism (SNP) **correlations with resistance to second-generation antipsychotics** (SGAs) in a real-world sample of patients with treatment-resistant mental disorders.

Conclusions:

A diagnosis of schizophrenia and the DRD2 rs1799732, DRD3 rs6280, and HTR2A rs7997012 genotypes **can predict high treatment resistance to SGAs**

Genomic medicine

10 August 2022

By **Adam Jameson**, **Beth Fylan**, **Greg Bristow**, **Alastair Cardno**, **Caroline Dalton**, **Gurdeep S Sagoo**, **Jaspreet Sohal** & **Samantha L McLean**

Corresponding author **Adam Jameson**

Pharmacogenomics is the future of prescribing in psychiatry

Patients' pharmacogenetic data could be used to improve adherence to antipsychotic medication by increasing the likelihood of therapeutic response and reducing the prevalence of adverse drug reactions.

Barriers	Enablers
Cost or funding	General interest in pharmacogenomics
Lack of knowledge about pharmacogenomics	Belief that pharmacogenomics will lead to precision medicine
Issues integrating pharmacogenomics into current workflows	Perception that pharmacogenomics can aid the clinician–patient relationship
Risk of misinterpreting results from pharmacogenomic tests	Belief that pharmacogenomics will become a standard part of care
Fear of discrimination owing to pharmacogenomics test results	Perception that pharmacogenomics can reduce adverse drug reactions
Fear that pharmacogenomic results could replace clinical judgement	Belief that pharmacogenomics can be useful for patients with treatment failure
A lack of clear guidance on the use of pharmacogenomics in psychiatry	Low risk of psychological distress in patients receiving pharmacogenomic results

In the future, we believe that pharmacogenomics will be a routine clinical factor that is assessed when making prescribing decisions